REMARKS

Claims 1-31 are pending herein. By this Amendment, Claims 1-2, 4-6, 8, 10, and 18-24 are amended, and new Claims 25-31 are added. The claim amendments are shown on the enclosed "Version with Markings to Show Changes Made." Support for the claim amendments is found in the specification at, *inter alia*, page 10, line 10 - page 15, line 16 and in the Examples. No new matter is added by this Amendment.

Applicants respectfully request the Examiner to initial and return Form PTO-1449 filed with an Information Disclosure Statement on April 3, 2001.

I. FORMAL MATTERS

Claim 2 was rejected under 35 U.S.C. 112, second paragraph, as assertedly being indefinite. Claim 2 is amended to delete the parenthetical expression, thereby rendering the rejection moot. Claims 18-24 have also been amended to delete parenthetical expressions. Reconsideration and withdrawal of the rejection are respectfully requested.

II. REJECTIONS OVER INABA ET AL.

Claim 1 was rejected under 35 U.S.C. 102(e) over Inaba et al. (U.S. Patent No. 6,040,434). Claim 1 was also rejected under 35 U.S.C. 103(a) over Inaba et al. These rejections are respectfully traversed.

Inaba discloses that aldehyde oxidase inhibitors, such as esculetin, may be used to reduce AMT formation during therapy with AZT. Derivatives of aldehyde oxidase inhibitors, such as esters, provide controlled release preparations of the inhibitors (col. 3, lines 4-9). Inaba does not teach or suggest a controlled-release oral preparation comprising esculetin or its derivative shown by the formula (I) and a gel-forming polymer

base, as recited in Claim 1. Thus, it would not have been obvious for one of ordinary skill in the art to make the claimed controlled-release oral preparation in view of the teachings of Inaba. Reconsideration and withdrawal of the rejections are respectfully requested.

III. SECOND REJECTION UNDER 35 U.S.C. 103(a)

Claims 1-24 were rejected under 35 U.S.C. 103(a) over Savastano et al. (U.S. Patent No. 5,681,584) in view of Watanabe et al. (U.S. Patent No. 5,455,268) and Hashimoto et al. (U.S. Patent No. 5,574,062). This rejection is respectfully traversed.

Savastano discloses a drug delivery device comprising: (1) a solid core comprising an active agent; (2) a delay jacket coated over the core; (3) a semi-permeable membrane coated over the delay jacket; and (4) optionally an enteric coating over the semi-permeable membrane (col. 5, lines 30-45). The active agent may be a 5-lipoxygenase inhibitor (col. 6, lines 33-35). The delay jacket may contain ethylcellulose or hydroxypropyl methylcellulose. The entire objective of Savastano is to deliver a drug to a pre-selected region of the gastrointestinal tract, particularly the colon, in order to treat diseased colonic tissue (e.g., inflammatory bowel disease, colitis ulcerosa, enteritis, regionalis Chron, chronic nonspecific colitis, and diverticulitis). See col. 1, lines 25-65.

Savastano does not disclose esculetin or any derivative thereof. Thus, Savastano does not teach or suggest a controlled-release oral preparation comprising esculetin or its derivative and a gel-forming polymer base, as recited in Claim 1. Further, Savastano does not teach or suggest (1) an enteric capsule containing a granulated mixture of esculetin or its derivative and a gel-forming polymer base, or (2) an enteric coating sprayed on a compressed mixture of esculetin or its derivative and a gel-forming polymer base.

Watanabe and Hashimoto do not overcome the deficiencies of Savastano. Watanabe discloses esculetin derivatives and pharmaceutical compositions as agents for protecting cartilage, for example, in patients with rheumatoid arthritis or osteoarthritis. There is no teaching or suggestion to substitute esculetin or its derivatives, which are used for protecting cartilage according to Watanabe, in the drug delivery device of Savastano, which is used for treating diseased colonic tissue. Any such combination is based upon hindsight reconstruction using the claimed controlled-release oral preparation as a template.

Moreover, Hashimoto *teaches away* from esculetin as an inhibitor of 5-lipoxygenase (col. 2, lines 55-64). In view of Hashimoto, one of ordinary skill in the art would have been led to use coumarin derivatives, which are disclosed to have greater inhibition activity on 5-lipoxygenase. Teaching away from a claimed invention is a per se demonstration of lack of *prima facie* obviousness. In addition, Watanabe and Hashimoto do not teach or suggest: (1) an enteric capsule containing a granulated mixture of esculetin or its derivative and a gel-forming polymer base or (2) an enteric coating sprayed on a compressed mixture of esculetin or its derivative and a gel-forming polymer base.

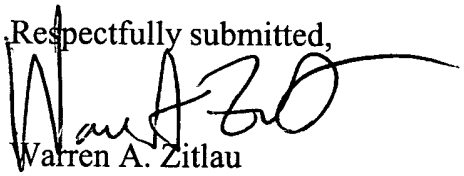
Accordingly, it is not seen why one of ordinary skill in the art, faced with the teachings of Savastano, would turn to the compositions of Watanabe or Hashimoto and include esculetin in the composition of Savastano. Even if the references were properly combinable, which they are not, Applicants' claimed invention would not be obtained. Thus, it would not have been obvious for one of ordinary skill in the art to make the claimed controlled-release oral preparation in view of the teachings of Savastano,

Watanabe, and Hashimoto. Reconsideration and withdrawal of the rejection are respectfully requested.

IV. CONCLUSION

In light of the foregoing remarks, this application is in condition for allowance, and early passage of this case to issue is respectfully requested. If there are any questions regarding this Amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application. Enclosed is a check for $126.00 for additional claim fee. If any other fees are due, please charge our Deposit Account No. 501032 (Docket No. FJIN-109).

Respectfully submitted,



Warren A. Zitlau
Registration No. 39,085

Barry I. Hollander
Registration No. 28,566

Hollander Law Firm, P.L.C.
Suite 305, 10300 Eaton Place
Fairfax, Virginia 22030
Tel: (703) 383-4800
Fax: (703) 383-4804

November 19, 2002

Enclosure:
Version with Markings to Show Changes Made
Check for $126.00

CERTIFICATE OF MAILING

I hereby certify that this correspondence dated 11/19/02 is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on 11/19/02.

Phyllis O Caldwell

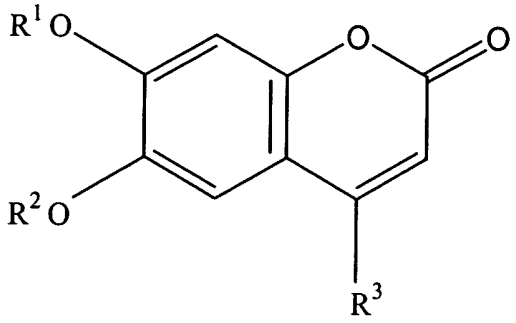
HOLLANDER LAW FIRM, P.L.C.
Suite 305
10300 Eaton Place
Fairfax, Virginia 22030

Date: 11/19/02

Version with Markings to Show Changes Made

Claims 1-2, 4-6, 8, 10, and 18-24 are amended as follows:

1. (Twice Amended) A controlled-release oral preparation comprising: esculetin, or its derivative shown by the formula (I),



(I)

wherein R^1 and R^2 are individually a hydrogen atom or a saturated or unsaturated aliphatic acyl group having 2-25 carbon atoms or a benzoyl group, and R^3 is a hydrogen atom, hydroxyl group, alkyl group, aryl group, or aralkyl group, or a pharmaceutically acceptable salt thereof as an effective component, and

a gel-forming polymer base.

2. (Amended) The controlled-release oral preparation of esculetin according to claim 1, containing 0.5 to 90 wt % [(hereinafter referred to as "%")] of [a] the gel-forming polymer base.

4. (Amended) The controlled-release oral preparation of esculetin according to claim 1, containing 0.5 to [50%] 50 wt % of an enteric coating base.

5. (Amended) The controlled-release oral preparation of esculetin according to claim 4, wherein the enteric coating base is selected from the group consisting of hydroxypropylmethylcellulose acetate succinate, hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, carboxymethylethylcellulose, [or] and methacrylic acid copolymer.

6. (Amended) The controlled-release oral preparation of esculetin according to claim 1, containing 0.5 to [50%] 50 wt % of an insoluble coating base.

8. (Amended) The controlled-release oral preparation of esculetin according to claim 6, comprising 0.5 to [90%] 90 wt % of a gel-forming polymer base, and 0.5 to [50%] 50 wt % of an enteric coating base and/or 0.5 to [50%] 50 wt % of an insoluble coating base.

10. (Twice Amended) The controlled-release oral preparation of esculetin according to claim 1, of which the release of esculetin is controlled so that the period of time required for the preparation to dissolve [80%] 80 wt % of esculetin is 0.5 to 23 hours as determined by the dissolution test according to the paddle method of the Japanese Pharmacopoeia [(paddle method)].

18. (Amended) The controlled-release oral preparation of esculetin according to claim 2, of which the release of esculetin is controlled so that the period of time required for the preparation to dissolve [80%] 80 wt % of esculetin is 0.5 to 23 hours as

determined by the dissolution test according to the paddle method of the Japanese Pharmacopoeia [(paddle method)].

19. (Amended) The controlled-release oral preparation of esculetin according to claim 3, of which the release of esculetin is controlled so that the period of time required for the preparation to dissolve [80%] 80 wt % of esculetin is 0.5 to 23 hours as determined by the dissolution test according to the paddle method of the Japanese Pharmacopoeia [(paddle method)].

20. (Amended) The controlled-release oral preparation of esculetin according to claim 4, of which the release of esculetin is controlled so that the period of time required for the preparation to dissolve [80%] 80 wt % of esculetin is 0.5 to 23 hours as determined by the dissolution test according to the paddle method of the Japanese Pharmacopoeia [(paddle method)].

21. (Amended) The controlled-release oral preparation of esculetin according to claim 5, of which the release of esculetin is controlled so that the period of time required for the preparation to dissolve [80%] 80 wt % of esculetin is 0.5 to 23 hours as determined by the dissolution test according to the paddle method of the Japanese Pharmacopoeia [(paddle method)].

22. (Amended) The controlled-release oral preparation of esculetin according to claim 6, of which the release of esculetin is controlled so that the period of time required for the preparation to dissolve [80%] 80 wt % of esculetin is 0.5 to 23 hours as

determined by the dissolution test according to the paddle method of the Japanese Pharmacopoeia [(paddle method)].

23. (Amended) The controlled-release oral preparation of esculetin according to claim 7, of which the release of esculetin is controlled so that the period of time required for the preparation to dissolve [80%] 80 wt % of esculetin is 0.5 to 23 hours as determined by the dissolution test according to the paddle method of the Japanese Pharmacopoeia [(paddle method)].

24. (Amended) The controlled-release oral preparation of esculetin according to claim 8, of which the release of esculetin is controlled so that the period of time required for the preparation to dissolve [80%] 80 wt % of esculetin is 0.5 to 23 hours as determined by the dissolution test according to the paddle method of the Japanese Pharmacopoeia [(paddle method)].

New Claims 25-31 are added.